Out-of-Hospital Continuous Positive Airway Pressure Ventilation Versus Usual Care in Acute Respiratory Failure: A Randomized Controlled Trial

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Study objective: Continuous positive airway pressure ventilation (CPAP) in appropriately selected patients with acute respiratory failure has been shown to reduce the need for tracheal intubation in hospital. Despite several case series, the effectiveness of out-of-hospital CPAP has not been rigorously studied. We performed a prospective, randomized, nonblinded, controlled trial to determine whether patients in severe respiratory distress treated with CPAP in the out-of-hospital setting have lower overall tracheal intubation rates than those treated with usual care.

Methods: Out-of-hospital patients in severe respiratory distress, with failing respiratory efforts, were eligible for the study. The study was approved under exception to informed consent guidelines. Patients were randomized to receive either usual care, including conventional medications plus oxygen by facemask, bag-valve-mask ventilation, or tracheal intubation, or conventional medications plus out-of-hospital CPAP. The primary outcome was need for tracheal intubation during the out-of-hospital/hospital episode of care. Mortality and length of stay were secondary outcomes of interest.

Results: In total, 71 patients were enrolled into the study, with 1 patient in each group lost to follow-up after refusing full consent. There were no important differences in baseline physiologic parameters, out-of-hospital scene times, or emergency department diagnosis between groups. In the usual care group, 17 of 34 (50%) patients were intubated versus 7 of 35 (20%) in the CPAP group (unadjusted odds ratio [OR] 0.25; 95% confidence interval [CI] 0.09 to 0.73; adjusted OR 0.16; 95% CI 0.04 to 0.7; number needed to treat 3; 95% CI 2 to 12). Mortality was 12 of 34 (35.3%) in the usual care versus 5 of 35 (14.3%) in the CPAP group (unadjusted OR 0.3; 95% CI 0.09 to 0.99).

Conclusion: Paramedics can be trained to use CPAP for patients in severe respiratory failure. There was an absolute reduction in tracheal intubation rate of 30% and an absolute reduction in mortality of 21% in appropriately selected out-of-hospital patients who received CPAP instead of usual care. Larger, multicenter studies are recommended to confirm this observed benefit seen in this relatively small trial. [Ann Emerg Med. 2008;52:232-241.]

0196-0644/$-see front matter

doi:10.1016/j.annemergmed.2008.01.006

INTRODUCTION

Respiratory distress is a common and important presentation to emergency medical services (EMS), for which outcome studies must be done to validate out-of-hospital interventions.[1,2] Individuals at the severe end of this spectrum whose respiratory efforts are failing are in need of some degree of immediate ventilatory support. Such patients usually receive positive-pressure ventilation by bag-valve-mask ventilation or tracheal intubation in the out-of-hospital setting before their arrival at an emergency department (ED). Out-of-hospital intubation attempts in non–cardiac arrest patients are less successful and have higher rates of aspiration of gastric contents than those performed in the ED.[3,4] In addition, patients arriving at an ED already intubated may be more likely to remain so, thus exposing them to the risk of nosocomially acquired pneumonia while being mechanically ventilated in an ICU, potentially doubling their mortality risk.[5,6]

Editor's Capsule Summary

What is already known on this topic

Application of continuous positive airway pressure (CPAP) for patients with acute respiratory distress reduces the need for tracheal intubation and mechanical ventilation. Case series have demonstrated CPAP's feasibility in out-of-hospital settings.

What question this study addressed

Seventy-one out-of-hospital patients with severe respiratory distress, randomized to receive CPAP or usual care, were assessed to determine need for tracheal intubation and mortality.

What this study adds to our knowledge

Within the CPAP group, the rate of intubation was 30% less than the usual care group, and mortality was 20% lower.

How this might change clinical practice

Emergency medical services systems and their medical directors should consider making CPAP available as part of the treatment for out-of-hospital severe respiratory distress patients, particularly in systems with long transport times.

Noninvasive ventilation using the modes of CPAP, pressure support ventilation, bilevel positive airway pressure, or noninvasive positive pressure ventilation is recommended in patients with respiratory disorders who remain in acute respiratory failure despite conventional therapy before invasive mechanical ventilation is considered.[7,8] In appropriately selected ED patients, this results in an early improvement in cardiorespiratory status, decreases the need for subsequent tracheal intubation, and reduces mortality.[9-23] Noninvasive ventilation using CPAP has shown the most benefit in acute cardiogenic pulmonary edema patients, but those with other causes of acute respiratory failure, including exacerbations of chronic obstructive pulmonary disease and asthma, benefit also. A recent meta-analysis of trials comparing patients with acute respiratory failure treated with noninvasive ventilation to those receiving tracheal intubation demonstrated significantly lower rates of pneumonia in the noninvasive ventilation group.[24]

Although it may be desirable to avoid tracheal intubation and its potential complications for acute respiratory failure patients by using CPAP in the out-of-hospital setting, it is not known whether the hospital-demonstrated benefits of CPAP are mitigated by the unique problems presented by the out-of-hospital environment (eg, diagnostic uncertainty, transport time pressures, gear damage from frequent transport, lack of bedside physician oversight). The evidence for CPAP in the out-of-hospital setting is limited only to several case series and 1 nonrandomized study.[25-31] There is an ethical, scientific, and fiscal imperative to require that therapies shown to be efficacious in hospitals be evaluated in the out-of-hospital setting to ensure their effectiveness before their introduction.[32,33] The purpose of this study was to determine whether out-of-hospital CPAP reduced the subsequent need for out-of-hospital or inhospital tracheal intubation in patients in severe respiratory distress who paramedics assessed as requiring some degree of out-of-hospital positive-pressure ventilatory support.

MATERIALS AND METHODS

Study Design

This prospective, randomized, controlled, nonblinded trial was registered with ClinicalTrials.gov (identifier NCT00405314).

Setting

The trial was conducted between July 2002 and March 2006. EMS in the study region are provided under a public utility model in which the government owns all ambulances and equipment and provides fully integrated medical oversight, including continuous online physician coverage. The regulator (government agency) oversees a single contractor who provides out-of-hospital services under the terms of a performance-based contract. There is 1 computer-assisted dispatch center for the entire province. The population of the study region is approximately 400,000, with paramedics responding to approximately 24,000 urgent calls annually, about 10% of these for mild to severe "breathing problems." Greater than 90% of ambulances in the region are staffed with advanced life support capable crews and have related equipment. Rapid sequence intubation is not within the scope of practice of our ground advanced life support medics; they are trained to facilitate non–cardiac arrest intubation, with topical anesthesia and small titrating doses of midazolam. In the year before commencement of this study, the out-of-hospital tracheal intubation success rate was 96% and 80% in cardiac arrest and non–cardiac arrest patients, respectively. The computer-assisted dispatch system facilitates a tiered response so that when a call is received for a person with respiratory difficulty, advanced life support paramedics are dispatched to the scene.

Ninety-six paramedics underwent a comprehensive education program concerning the ethical conduct of research and the study protocols. This included a didactic session on the principles of ethical research and on the treatment of acute respiratory failure. Paramedics then demonstrated the use of CPAP on one another and were subsequently "signed off" after passing a practical test on the identification, enrollment, and treatment of study patients. Shorter refresher sessions were incorporated into the paramedics' usual ongoing training throughout the study period. These included periodic, unannounced case simulations with on-duty crews in a mobile, high-fidelity simulator, conducted by the study investigators. Laminated cards detailing the eligibility criteria, consent process, and randomization and treatment protocols were included with every set of CPAP equipment.

Table 1. Inclusion/exclusion criteria.

Study Eligibility	Respiratory Distress	LOC	Cardiac Hemodynamic Status	Logistics	Age, y	Advanced Directive
Inclusion criteria	Severe respiratory distress with failing respiratory efforts (paramedic judgment) Accessory muscle use Respiration rate >25 breaths/min Hypoxia	Normal LOC Understand and cooperate with CPAP application if allocated	Stable No chest pain within 3 h	Trip destination of participating hospital Enough portable O_2	≥16	None
Exclusion criteria	Respiratory arrest or near arrest (paramedic judgment) Respiration rate <8 breaths/min Periods of apnea	Decreased LOC Loss of protective airway reflexes	Ongoing cardiac ischemia Hypotensive with evidence of end-organ hypoperfusion (paramedic judgment)	Trip destination of nonparticipating hospital Not enough portable O_2 to make transport	<16	Do not resuscitate

LOC, Level of consciousness.

Selection of Participants

All patients presenting to advanced life support paramedics with acute respiratory distress during the study period were assessed for eligibility for participation in the study. Inclusion/exclusion criteria were based on the following characteristics: degree of respiratory distress, level of consciousness, cardiohemodynamic status, logistics, age, and presence of an advanced directive (Table 1). We specifically selected the severest subset of the out-of-hospital "shortness of breath" cohort to allow valid statistical comparisons between the 2 treatment groups with regard to the primary outcome of interest, tracheal intubation. To include patients with less severe respiratory distress would have rendered it logistically impossible to power the study to show a difference in a meaningful patient-oriented outcome. Patients had to have a trip destination of the QEII Health Sciences Center (academic tertiary care center with approximately 65,000 visits annually) or Dartmouth General Hospital (regional community hospital with approximately 45,000 visits annually).

The consent process used in this study has been described in detail elsewhere.[34] Briefly, our institutional research ethics board approved enrollment of patients under an exception to informed consent under the stipulations of Section 2.8 of the Tri-Council Policy Statement: Ethical conduct for research involving humans.[35] Patients meeting eligibility criteria were read a standard statement that briefly explained the nature of the study, and if they (or any family members present) did not refuse participation, they were enrolled. This statement did not suggest that CPAP may alter tracheal intubation rates, only that the 2 treatments were being compared as ventilatory adjuncts. Full informed consent was obtained from patients or their surrogates as soon as was practically possible.

Interventions

Once a patient was deemed eligible for the study, paramedics contacted their dispatcher by radio, who then randomly assigned the patient to one of 2 treatment groups: usual care (including bag-valve-mask ventilation with or without tracheal intubation) or CPAP. The randomization sequence was generated from a random-numbers table. A customized tool was created that permitted sequential exposure to the allocation sequence through the use of numbered, opaque stickers that prohibited determination of the sequence until after the sticker had been completely removed. When paramedics enrolled a patient into the study, they contacted the dispatcher with a request for randomization. The dispatcher removed 1 sticker (in sequence) to reveal the allocation, which was then communicated to the paramedic by radio. This approach maintained the integrity of the allocation sequence. Both the paramedic and the dispatchers remained blinded to the allocation until after the patient had been enrolled, thus reducing selection bias.

Patients in both groups otherwise received standard protocol-driven therapy for severe respiratory distress,[36] as guided by the patients' clinical condition and presumed diagnosis. In the field, this could include nitroglycerin, furosemide (only if the patient was already receiving the drug *and* demonstrated evidence of volume overload), and morphine (low dose) for congestive heart failure, and β-2 agonists (salbutamol), and ipratropium bromide for chronic obstructive pulmonary disease and asthma. Oxygen delivered by face mask, bag-valve-mask ventilation, and tracheal intubation were applied according to need. In general, paramedics use the following explicit indications to guide their judgment in the need for intubation: (1) the need to obtain or maintain a patent airway where there is a mechanical obstruction (eg, severe angioedema) or functional obstruction (eg, tongue blocking hypopharynx in the setting of a profound decrease in level of consciousness), (2) need to protect the airway if there is loss of protective reflexes (eg, decreased level of consciousness, leading to loss of cough and swallow reflexes), or (3) the need to correct a severe gas exchange problem (eg, asthma or pulmonary edema, leading to progressive hypoxia or

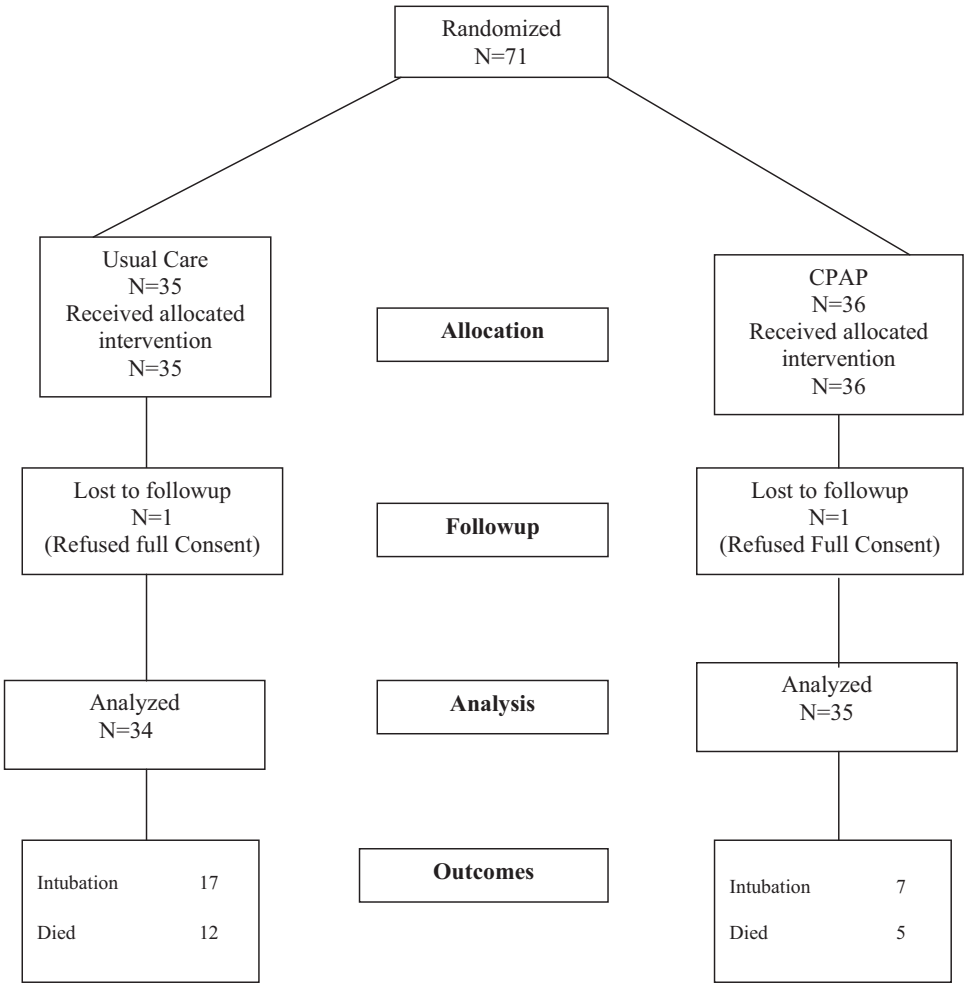

Figure 1. Patient flow through the study.

hypercapnia) in the setting of failing respiratory efforts. Even when there is an indication for intubation, the paramedic must then also weigh the risks and benefits of intubating out-of-hospital (versus bag-valve-mask ventilation and transport) by considering predictors of difficulty and presumed transport time.[37]

Patients assigned to the CPAP group received 10 cm H_2O CPAP through a facemask fitted with a CPAP valve and controlled with a portable flow generator (Whisperflow; Respironics Agile Medical, Prospect Park, PA, unrestricted equipment loan). The use of CPAP outside the study protocol was forbidden and strictly controlled. Patients in the CPAP group were intubated in the out-of-hospital phase if they met any of the following criteria: progressively worsening pulse oximetry despite effective CPAP, loss of airway protective reflexes (cough, swallow), decreased level of consciousness, ECG or clinical evidence of cardiac ischemia, hemodynamic instability, intolerance/poor fit of facemask, paramedic clinical impression of deterioration, or patient request.

Once in the ED, all patients were treated at the discretion of the attending emergency physician and subsequent admitting physician, including the continuation of CPAP therapy if indicated. The decision to intubate after arrival in the ED was left to the judgment of the treating physician.

Given our strict inclusion criteria, we expected many patients in the usual care group to be intubated in the out-of-hospital phase of their care. According to local paramedic airway education and management practices, eligibility criteria, and estimates from the literature, we expected that 87.5% of patients in the usual care group would require tracheal intubation at some time in their out-of-hospital/hospital treatment versus 50% in the CPAP group. This yielded a required sample size of 28 patients in each group to detect a 37.5% difference in tracheal intubation rate, with a power level of 0.8 and an α level of 0.95. To account for anticipated attrition in this relatively sick population, an additional 25% were enrolled. The unit of analysis was the unique patient encounter (ie, 3 patients were enrolled more than once in the study). The main diagnoses were dichotomized (eg, CHF present=1; absent=0) at each stage of care (ie, out-of-hospital, ED, and admission). All of the continuous variables (eg, age, length of stay) were retained as such (ie, none were categorized).

The primary outcome (proportion intubated) was analyzed on an intention-to-treat basis with a χ^2 test for the unadjusted estimate of effect.

Multiple logistic regression modeling was performed to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the primary outcome. The multivariable model included covariates representing severity on presentation (out-of-hospital respiratory rate and pulse oximetry); an ED diagnosis other than chronic obstructive pulmonary disease, CHF, or asthma (ie, diagnoses that may not benefit from CPAP, thus with the potential to influence estimates of effect, specifically pneumonia or acute coronary syndrome); age; and sex. The model development was based on knowledge from existing literature, as well as clinical experience. We used bootstrap resampling methods with 1,000 iterations of the multivariable analysis to validate the inclusion of significant variables. Variables that remained significant ($P<.1$) in more than 50% of the analyses were included in the final model. Descriptive data analyses were conducted using Stata statistical software, version 7 (StataCorp, College Station, TX) and regression modeling was conducted using S-Plus (version 8.0.4) and the Design Library developed by Alzola and Harrell.[38] The study was insufficiently powered to evaluate the effect of all possible interaction terms or to conduct regression analyses on the secondary outcome of mortality.

Data Collection and Processing

On arrival to the ED with a study patient, paramedics dropped their record of the out-of-hospital encounter into a specially designated locked box. A research nurse checked this box Monday through Friday and alerted the study investigators to new patients. A study investigator (J.T. or D.A.P.) then visited the patient or their family to obtain full informed consent. If consent was secured, a research nurse unblinded to the purpose of the study abstracted data about the patient's out-of-hospital and hospital course onto a standard data collection form after the patient either left hospital or died. At the end of the study a research nurse blinded to both the purpose of the study and treatment allocation verified the outcome data with the original charts. Outcome data were entered into an Access database.

Outcome Measures

The primary outcome measure was the need for tracheal intubation from the time of accessing medical care to inhospital death or discharge. Secondary outcome measures included critical care unit length of stay, hospital length of stay (until death or discharge), and mortality.

A data safety and monitoring board met to review the study after every 8 patients were enrolled. Only 1 minor change to the study protocol was required according to this ongoing review: the addition of "any chest pain within 3 hours" to the initial exclusion criteria of "ongoing cardiac ischemia." This was meant to be a more explicit, conservative response to the suggestion in one study[39] that CPAP may be associated with an increased risk of cardiac ischemia in certain patient presentations.

Table 2. Baseline characteristics (mean [SD] unless otherwise noted).*

Characteristics	Usual Care, N=34	CPAP, N=35
Age, y, median	70.5	69
Sex, % female	41.2	57.1
Respiratory rate, breaths/min	37.6 (6.1)	38.2 (8.0)
SpO_2, %*	75.0	81.5
Pulse rate, beats/min	121.2 (23.8)	112.4 (25.2)
Systolic blood pressure, mm Hg	157.3 (42.6)	162.9 (37.9)
On-scene time, min	21.1 (9.3)	22.2 (7.4)
Total out-of-hospital time, min	43.8 (12.4)	41.3 (12.8)
Out-of-hospital clinical impression of CHF, chronic obstructive pulmonary disease or asthma	33	34

*Median values reported for variables that were not normally distributed.

RESULTS

A total of 71 patients were randomized, 35 into usual care and 36 into CPAP (Figure 1). Two patients (1 in each group) refused the ongoing use of their data once their condition stabilized. The remaining 69 patients were followed until death in hospital or discharge. Two patients were enrolled in the study twice: one was randomized to usual care both times and the second was randomized to CPAP both times. Neither was subsequently intubated. One patient was enrolled 6 times, 4 times to CPAP and twice to usual care, and was not intubated at any time. Despite the fact that treatment allocation was randomized, to account for any potential bias from these repeated patients we analyzed the results, including all care episodes for all patients and including only the first enrollment of the repeated patients. The results and significance of all analyses were similar regardless of whether or not all repeated patients' visits were included, and so the results are reported for all 69 patient encounters.

Overall, each treatment group was similar in terms of demographics and baseline physiologic characteristics (Table 2). As expected, patients were initially in significant respiratory distress, with high respiratory rates and low oxygen saturations. The groups were balanced with regard to mean total out-of-hospital intervals (call receipt to hospital arrival) and mean scene intervals (arrival of ambulance on scene to depart scene).

Both groups had similar proportions of patients with exacerbations of CHF, chronic obstructive pulmonary disease, or asthma. There was 1 out-of-hospital misdiagnosis: a patient in the CPAP arm labeled as having CHF but diagnosed as having chronic obstructive pulmonary disease in the ED. A further 30 patients (16 in the CPAP arm, 14 in the usual care arm) had an additional diagnosis added to the out-of-hospital clinical impression. In the majority of these cases, the diagnosis of CHF was added to chronic obstructive pulmonary disease (or

Table 3. Cause of severe respiratory distress.

Cause	Out-of-Hospital Clinical Impression		In-ED Diagnosis		Primary ED Diagnosis of CHF, COPD, or Asthma	Contributing Diagnosis of ACS, Pneumonia, or Other
CPAP	CHF	24	CHF	23		
n=35	COPD	7	COPD	13	35 (100%)	13 (37%)
	Asthma	5	Asthma	5		
	SOB NYD	1	Pneumonia	4		
	Pneumonia	1	ACS	7		
			Other	2		
Usual care	CHF	20	CHF	23		
n=34	COPD	10	COPD	14	33 (97%)	12 (35%)
	Asthma	6	Asthma	5		
	SOB NYD	1	Pneumonia	9		
			ACS	2		
			Other	1		

CHF, Congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *ACS,* acute coronary syndrome; *SOB*, shortness of breath; *NYD,* not yet diagnosed. The number of diagnosis is greater than the number of patients because of multiple diagnoses in some patients.

Table 4. Outcome measures.

Outcome measures	Usual Care, N=34 (%)	CPAP, N=35 (%)
Intubated, No.	17 (50)	7 (20)
Hospital length of stay (median days)	9	7
Critical care unit length of stay (median days)	3	6.5
Admitted to a critical care unit, No.	16 (47.1)	13 (37.1)
Mortality	12 (35.3)	5 (14.3)

vice versa); however, in some cases a diagnosis of pneumonia or acute coronary syndrome was added (Table 3).

In only 1 case was the primary diagnosis in the ED not CHF, chronic obstructive pulmonary disease, or asthma; it occurred in the usual care arm (primary diagnosis of pneumonia). Out-of-hospital interventions were similar between the 2 groups and followed protocol in 68 of 69 patients. For example, when the out-of-hospital clinical impression was CHF, sublingual nitroglycerine was used in 38 of 44 (86.4%), furosemide in 21 of 44 (47.7%), and low-dose morphine in 11 of 44 (25%) patients in equal proportions in the 2 groups (for individual patient intervention and diagnosis, see Figure E1, available online at http://www.annemergmed.com). One patient in the CPAP arm received an incorrect medication (nitroglycerine) according to an incorrect clinical impression of CHF in the field. In the ED, medications for both groups were appropriate in relation to the diagnosis and similar between the 2 groups.

For the primary outcome analysis on an intention-to-treat basis, 17 of 34 (50%) patients were intubated in the usual care group versus 7 of 35 (20%) in the CPAP group (unadjusted OR 0.25; 95% CI 0.09 to 0.73). The protective effect of CPAP remained statistically significant after adjustment (adjusted OR 0.16; 95% CI 0.04 to 0.7). These data suggest that 3 (95% CI 2 to 12) patients in severe respiratory distress requiring out-of-hospital ventilatory support need to be treated with out-of-hospital CPAP to prevent 1 intubation (Tables 4 and 5).

Fewer CPAP patients died than usual care patients (5/35 [14.3%] versus 12/34 [35.3%] respectively; OR 0.3; 95% CI 0.09 to 0.99). Recalculating the tracheal intubation and mortality rates using the worst-case scenarios for the 2 individuals who withdrew the use of their data (ie, that the individual receiving usual care was neither intubated nor died and that the individual receiving CPAP was intubated and died) yields ORs of 0.30 (95% CI 0.11 to 0.85) and 0.38 (95% CI 0.13 to 1.18), respectively. Thus, the main conclusion of the study with regard to the primary outcome is unchanged. There were no statistically significant differences between the treatment groups for length of stay either inhospital or in a critical care unit (Table 4).

Nine patients in the usual care arm were intubated by paramedics before arrival in the ED. Of these 9, 1 had an out-of-hospital respiratory arrest followed by cardiac arrest (during which the patient was intubated) and was pronounced dead in the ED, 3 died inhospital, and 5 survived to discharge. Two patients randomized to usual care had an unsuccessful out-of-hospital intubation attempt. One of these patients had a successful intubation in the ED followed by a cardiac arrest in the ED but was resuscitated and survived to discharge, neurologically intact. The other had a successful tracheal intubation in the ED followed by an ICU admission and extubation and then died on a long-term-care ward 10 months later. There were no out-of-hospital intubations in the CPAP group. Figure 2 describes the location of tracheal intubation or death of all the patients in the study.

LIMITATIONS

There are a few limitations to this study worthy of discussion. The number of patients screened who met eligibility criteria and then were not enrolled or refused the initial consent process was not formally recorded (by informal measurement,

Table 5. ORs and 95% CIs for primary outcome of intubation in patients with acute respiratory failure.

Variables in Multivariable Model	Crude OR	95% CI	Adjusted OR*	95% CI
Allocation to CPAP	0.25	0.09–0.7	0.16	0.04–0.7
Sex, female	0.81	0.3–2.2	—	—
Age, y	1.0	1.0–1.04	—	—
Out-of-hospital SpO_2	0.94	0.9–1.0	0.37	0.2–0.9
Out-of-hospital respiratory rate, breaths/min	1.03	1.0–1.07	—	—
ED diagnosis of pneumonia	0.7	0.2–2.5	—	—
ED diagnosis of acute coronary syndrome	2.7	0.6–11.2	8.8	1.3–62.2

*Final model validated by bootstrapping procedure.

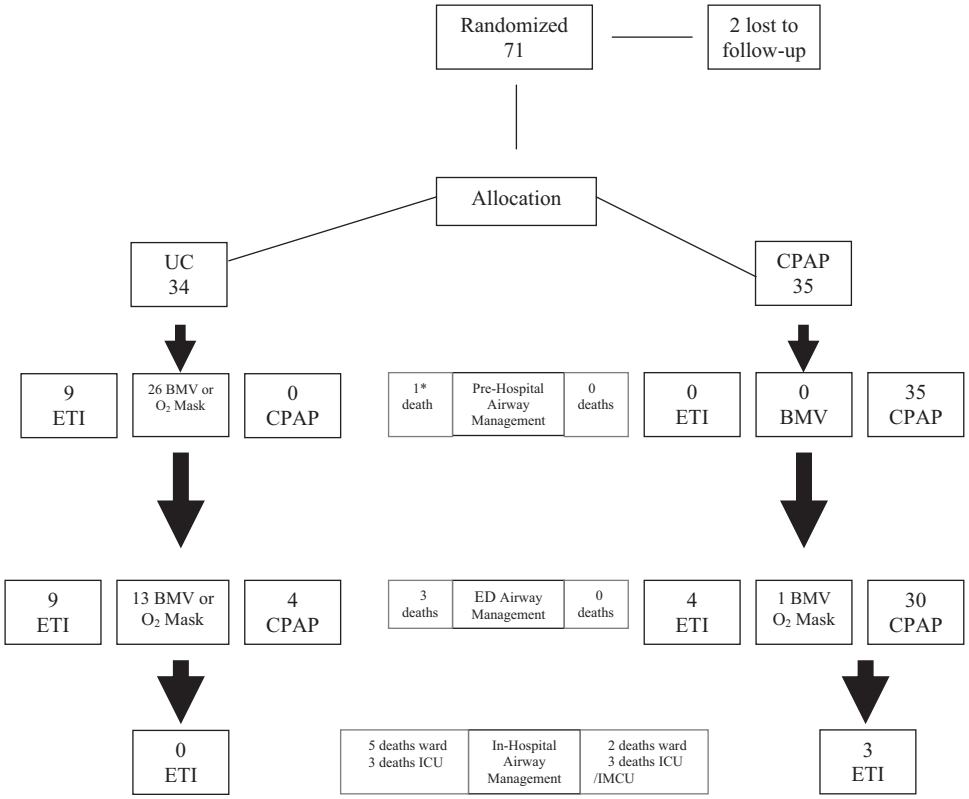

Figure 2. Location/time of tracheal intubation or death.

the number was small). Thus, we cannot exclude the possibility that initial refusers were somehow systematically different from study participants.

No validated severity of respiratory distress score[40,41] was used to determine eligibility, which, despite reflecting actual practice, may limit the comparability of this study with future studies using such scores. In addition, there were no absolute objective criteria for intubation. A degree of paramedic judgment was permitted because we believed that this was safer for the patients from a clinical point of view. Given that intubation is the primary outcome and that this is an unblinded study, this could bias the study results. We believe that the decision to leave a degree of judgment in the intubation decision up to the treating paramedic or subsequent physician was reasonable and ethical for the following reasons: (1) it more closely duplicates the actual working conditions and therefore may be more generalizable; (2) airway management education in our EMS system is based on the curriculum of a national airway course,[37] so intubation decisions are based on a sound knowledge of explicit first principles; (3) all paramedics received, as part of their training, a lecture on the absolute importance of research ethics to the integrity of a study; and

finally (4) many emergency physicians and most inhospital/ICU physicians were unaware of the existence or purpose of this out-of-hospital study.

The lower-than-expected difference in tracheal intubation rate between groups (30% actual versus 37.5% expected) reduces the statistical power of the study somewhat. Additionally, the overall tracheal intubation rates were lower than expected in both groups. One possible explanation is that the estimates of tracheal intubation rates were based largely on hospital data, highlighting the need for reliable out-of-hospital data. Another possibility is that during the study period the out-of-hospital airway management literature,[2,37] and therefore our paramedics' airway education, evolved toward less emphasis on tracheal intubation as the outcome of success (the technical imperative) and more emphasis on oxygenation/ventilation as the outcome of success (the clinical imperative), which may have resulted in paramedics performing fewer intubations overall in favor of rapid transport to hospital while performing bag-valve-mask ventilation.

As in similar inhospital studies done previously, we did not include a sham treatment and so the receiving emergency physician was not blinded to the treatment group. To do so was thought to be technically and operationally unfeasible. It is possible that this affected subsequent decisions about tracheal intubation, but we think this is unlikely.

The generalizability of our study is limited by the fact that, like other out-of-hospital CPAP studies, ours was conducted in an urban setting with generally short transport-to-hospital times. The CPAP devices we used required large reserves of high-pressure oxygen, which could limit the applicability of CPAP in a more rural setting. Finally, it is possible that the outcome was influenced by cointervention bias.

DISCUSSION

This prospective randomized comparison of out-of-hospital CPAP versus usual care for patients with severe respiratory distress shows a significant benefit for patients treated with CPAP with respect to need for subsequent intubation. To our knowledge, this is the first randomized controlled out-of-hospital study of the effectiveness of CPAP and the only one to include patients in severe respiratory distress from all causes.

Several reports document the out-of-hospital use of CPAP in patients with acute pulmonary edema. In the scientifically most rigorous of these, Hubble et al[27] compared the use of out-of-hospital CPAP with usual care for patients with acute pulmonary edema concurrently in 2 geographically adjacent EMS systems. Intubation rates were lower in their study (CPAP 9%; usual care 25%) than in our study (CPAP 20%; usual care 50%), likely reflecting the different spectrums of respiratory distress eligible for enrollment. To show a difference in a meaningful patient-oriented outcome (tracheal intubation rate), we intentionally limited eligibility for this study to patients at the severe end of the respiratory distress spectrum (ie, respiratory efforts failing and requiring immediate positive pressure ventilation). Although CPAP may plausibly bring some benefit to disease-oriented outcomes (improved O_2 saturation levels; decreased respiratory rate) in patients in the moderate to severe range of the spectrum, it would be hard to show a difference in the relatively low tracheal intubation rates in this group. Other case series have shown that paramedics can safely apply CPAP to patients in the out-of-hospital setting, but this was not directly addressed in our study.[28-30]

We deliberately did not restrict enrollment to one presumptive diagnostic class of patients (eg, acute pulmonary edema), given the high field misdiagnosis rate for respiratory distress (eg, 24% in the Hubble et al[27] study) and to maximize the generalizability of our results. Acute respiratory failure is the final common pathway of many types of hypoxic and hypercarbic insults, and given that the hospital-based literature shows a possible benefit of CPAP for both, we thought it was important that both be represented in our study sample. We achieved similar distributions of diagnosis in both arms, with CHF, chronic obstructive pulmonary disease, or asthma being the primary diagnosis in 68 of 69 (99%) of the cases overall.

The results also suggest a possible survival benefit for CPAP-treated patients, although the study was not powered to detect this. We believe that the 21% absolute difference in mortality is interesting and not inconsistent with inhospital CPAP studies.[16,23] We cannot exclude the possibility that other, unmeasured confounders may account for this observed trend, however. One possibility is that it was not only the positive effect of the out-of-hospital CPAP that improved outcomes but also that being randomized to the CPAP arm protected a patient from some negative effect of out-of-hospital intubation. Although our numbers are small, our results do not support this theory. The mortality rate in patients who had an out-of-hospital intubation attempt was 40%, which is similar to the mortality rate in the rest of the usual care cohort (33%). Even so, given the evolution of the out-of-hospital airway literature after the development of this study protocol, any future larger study should include a third arm in which bag-valve-mask ventilation is the only means of providing positive-pressure ventilation (ie, a non–tracheal intubation, non-CPAP arm) in the failing out-of-hospital severe respiratory distress patient.

Paramedics can be trained to use CPAP for patients in severe respiratory distress. There was an absolute reduction in tracheal intubation rate of 30% and an absolute reduction in mortality of 21% in appropriately selected out-of-hospital patients who received CPAP instead of usual care. Larger, multicenter studies are recommended to confirm the observed benefit seen in this relatively small trial.

The authors wish to acknowledge the paramedics of the Halifax Regional District, without whose dedication and enthusiasm the study would not have been possible. The following also contributed to the study: Corinne Burke; Norma Frank, RT; Daphne Murray, RN; Megan Crawford, RN; Paula Martell, RN, Data Safety and Monitoring Board, EMC Inc.; and Emergency Health Services Nova Scotia. Vaneeta Kaur-

Grover (PhD candidate and statistical consultant), Department of Mathematics and Statistics at Dalhousie University conducted the regression analyses.

Supervising editor: Theodore R. Delbridge, MD, MPH

Author contributions: JT, DAP, SA-S, and DJB conceived and designed the trial. JT, DAP, SA-S, and DJB obtained the funding. JT, DAP, SA-S, and DJB supervised the conduct of the trial and data collection. SA-S supervised management of the data, including quality control. JT, DAP, and DJB supervised the recruitment by paramedics. SA-S provided statistical advice on study design and statistical methodology and conducted descriptive data analyses. JT drafted the first copy of the article, and all authors contributed substantially to its revisions. JT and DAP take responsibility for the paper as a whole.

Funding and support: By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article, that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement. This study protocol was approved by Capital District Health Authority Research Ethics Board. Their file number is CDHA 2000-305, Clinical Trials.gov Identifier NCT00405314.

Publication dates: Received for publication February 6, 2007. Revisions received June 25, 2007, and October 18, 2007. Accepted for publication January 9, 2008. Available online April 3, 2008.

Presented at the International Congress of Emergency Medicine, June 2006, Halifax, Nova Scotia, Canada.

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Patient Characteristics				Pre-Hospital					In ED						Outcomes	
ID #	Age	Date Enrolled	Randomized To	RR	O_2 Sat %	Clinicial Impression	Highest Level of Airway Management	Meds	RR	O_2 Sat %	1st Diagnosis	2^{0} Diagnosis	Highest Level of Airway Management	Meds	Length of Stay (Days)	Live/Die
1	75	21-Jul-02	UC	40	60	CHF	ETI	N,F,M	tubed	92	CHF	none	Ventilator	N,F	ICU 5, Hosp 27	d/c alive
2	56	30-Jul-02	UC	34	88	CHF	ETI	N,F,M	tubed	96	CHF	none	Ventilator	N,F	ICU 2, Hosp 10	d/c alive
3	73	1-Sep-02	CPAP	44	76	CHF	CPAP	none	36	97	CHF	COPD	CPAP X 3Hrs	N,F,B,I,A,S	ICU 0, Hosp 16	d/c alive
4			refused long consent													
5	75	28-Sep-02	UC	48	80	CHF, Lung Cancer	BMV	N,B,I	32	98	CHF	COPD, Lung Ca	CPAP	N,B,I	ICU 0, Hosp 21	d/c alive
6	73	7-Oct-02	CPAP	30	50	CHF	CPAP	N	*	86	CHF	none	CPAP	N,F	ICU 2, Hosp 17	d/c alive
7	83	10-Dec-02	CPAP	30	58	CHF	CPAP	N,F	*	85	CHF	ACS	CPAP	N,F,M,A	ICU 0, Hosp 6	d/c alive
8	71	22-Dec-02	CPAP	40	82	COPD	CPAP	B	28	98	COPD	none	CPAP and O2 mask	B,I,N,A	overnite in ED, d/c	d/c alive
9	75	26-Dec-02	CPAP	36	*	CHF	CPAP	N	26	92	COPD	ACS	CPAP	B,I,S	ICU 0, Hosp 2	died in hospital
10	90	1-Jan-03	CPAP	36	79	CHF	CPAP	NONE	*	98	CHF	Sepsis	CPAP	N,F,A	ICU 0, Arrest on Floor (ETI)	died 21h in hosp, ETI at arrest
11	83	2-Mar-03	UC	34	86	CHF	ETI	N,B	*	99	CHF	none	Ventilator	N,F	ICU 3, Hosp 3	d/c alive
12	83	18-Mar-03	CPAP	36	50	CHF	CPAP	N	36	88	CHF	ACS	ETI	M	ICU 10, Hosp 10	d/c alive
13	61	21-Apr-03	CPAP	30	90	CHF	CPAP	N	24	99	CHF	COPD	CPAP	N,F,M,F,B,I	ICU 0, Hosp 11	d/c alive
14	59	15-May-03	UC	36	50	COPD	o2 by mask	NONE	40	*	COPD	CHF	O2 by mask	B,I,A,S,F	ICU 0, Hosp 7	d/c alive
15	72	5-Jun-03	CPAP	48	90	COPD	CPAP	B,I	40	94	COPD	none	CPAP	B,I,S	ICU 0, Hosp 2	die in hospital no ETI
16	79	13-Jun-03	CPAP	38	83	CHF,COPD	CPAP	N,F	22	82	CHF	COPD, ACS	CPAP	F, N	ICU 8, Hosp 17	d/c alive
17	82	26-Jun-03	CPAP	36	82	CHF	CPAP	N,F,M	32	100	CHF	ACS	CPAP	N,F	ICU 0, Hosp 8	d/c alive
18	62	28-Jun-03	CPAP	40	79	COPD	CPAP	NONE	20	93	COPD	none	CPAP	B,I,S	overnite in ED, d/c	d/c alive
19	61	1-Jul-03	UC	38	50	CHF	ETI	N,F	tubed	95	CHF	none	Ventilator	N,F,D	ICU 3, Hosp 8	d/c alive
20	58	15-Jul-03	CPAP	20	*	CHF	CPAP	N,F	34	95	CHF	none	CPAP	N,F	ICU 47, Hosp 58	d/c alive
21	27	29-Aug-03	UC	48	67	CHF	ETI	N	tubed	65	CHF	Primary pulmonary arterial hypertension	ETI	N,F,D	Died in ICU after 7,5 hours	death
22	68	8-Sep-03	UC	30	94	COPD	o2 by mask	B,I	30	87	COPD	Pneumonia	CPAP	B,I,S,A	ICU 0, Hosp 12	d/c alive
23	64	14-Sep-03	CPAP	38	74	CHF	CPAP	B	44	96	CHF	Pneumonia, COPD	CPAP	B,I, F,N,A	ICU 0, Hosp 9	d/c alive
24	refused long consent															
25	43	28-Nov-03	CPAP	50	74	Asthma	CPAP	B,I	24	93	Asthma	none	CPAP	B,I	ICU 0, Hosp 5	d/c alive
26	39	17-Dec-03	UC	40	85	Asthma	o2 by mask	B,I	24	92	Asthma	none	O2 by mask	B,S	time in ED, then d/c	d/c alive
27	79	10-Jan-04	UC	48	66	COPD	BMV, ETI attempt unsuccessful	B,I	*	84	COPD	Pneumonia	ETI	B,I,A	ICU 26, Hosp 298	die in hospital
28	85	10-Jan-04	CPAP	42	60	CHF	CPAP	N,F,M	32	75	CHF	none	CPAP	N,F,M	ICU 2, Hosp 11	d/c alive
29	83	6-Feb-04	UC	40	51	CHF	ETI	N,F	tubed	90	CHF	ACS	Ventilator	F,M,D	ICU 3, Hosp 0	die in ICU
30	79	17-Feb-04	UC	36	78	COPD	o2 by mask	B,I	*	100	COPD	ACS, CHF	ETI	S,I,D	ICU 1, Hosp 0	die in ICU
31	89	27-Feb-04	UC	36	*	CHF	BMV, ETI attempt unsuccessful	NONE	*	96	CHF	none	ETI	F,D	ICU 2, Hosp 24	d/c alive
32	88	28-Feb-04	UC	36	64	CHF	o2 by mask	N,M	24	88	CHF	COPD	O2 by mask	N,F, B,I,A	ICU 0, Hosp 4	d/c alive
33	79	18-Mar-04	CPAP	54	90	CHF	CPAP	N,F,B	38	99	CHF	none	CPAP	N	ICU 0, Hosp 5	d/c alive
34	43	23-Mar-04	UC	42	*	Asthma	o2 by mask	B,I	32	91	Asthma	none	O2 by mask	S,I,B	d/c home from ED	d/c from ED
35	71	11-Apr-04	CPAP	40	77	CHF	CPAP	N,F,B	38	*	CHF	none	CPAP	N,F,M,B,I	ICU 0, Hosp 5	d/c alive
36	69	16-Apr-04	CPAP	36	77	CHF	CPAP	N	44	93	CHF	none	ETI	N,F,D	ICU 0, Hosp 32	d/c alive
37	89	20-Apr-04	CPAP	40	86	CHF	CPAP	N,M,F	*	93	CHF	UTI	CPAP	N,F,A	ICU 0, Hosp 15	die in hospital
38	68	31-May-04	CPAP	28	98	CHF, Pneumonia	CPAP	N,B	23	100	CHF	Pneumonia	CPAP	F,A	ICU 0, Hosp 4	d/c alive
39	77	1-Jun-04	UC	44	60	CHF	o2 by mask	N,F,B	36	96	CHF	none	O2 by mask	N,F,B,M	ICU 0, Hosp 3	d/c alive
40	43	1-Jun-04	CPAP	32	88	Asthma	CPAP	B,I	40	100	Asthma	none	CPAP	B,I,S	ICU 0, Hosp 2	d/c alive
41	80	29-Jun-04	UC	36	67	CHF	o2 by mask	N,F,M	32	87	CHF	none	ETI	F,B,I,A	ICU 4, Hosp 122	d/c alive
42	86	19-Jul-04	CPAP	40	89	CHF	CPAP	B	*	97	CHF	none	CPAP	N,F	ICU 0, Hosp 20	d/c alive
43	44	16-Aug-04	CPAP	42	100	Asthma	CPAP	B,I	24	95	Asthma	none	CPAP	B,I,S	ICU 0, Hosp 2	d/c alive
44	68	10-Sep-04	CPAP	32	94	COPD	CPAP	B,I	*	99	COPD	none	CPAP	B,I,S,A	ICU 0, Hosp 3	d/c alive
45	77	7-Nov-04	UC	40	77	CHF	o2 by mask	N,B,F	42	95	CHF	none	O2 by mask	F,N	ICU 0, Hosp 83	died
46	59	22-Nov-04	CPAP	56	84	CHF	CPAP	N	44	99	CHF	ACS	CPAP	N,F	ICU 6, Hosp 6	d/c alive
47	79	29-Nov-04	UC	32	80	COPD, CHF	o2 by mask	N,F,M,V	40	80	COPD	CHF, Pneumonia	O2 by mask	N,F,A	ICU 0, Hosp 6	died
48	67	29-Nov-04	CPAP	30	95	COPD	CPAP	B,I	28	92	COPD	CHF	CPAP	B,I,F,N,S,A	ICU 0 Hosp 8	d/c alive
49	67	29-Dec-04	UC	24	62	COPD, CHF	BMV, ETI after Cardiac Arrest	N,F,B	tubed	*	CHF, COPD	none	Ventilator	NONE	Died in ED	Died in ED
50	39	4-Jan-05	CPAP	34	50	Asthma, CHF	CPAP	N,B	40	98	Asthma	Pneumonia	ETI	B,S	ICU 10, Hosp 0	died in ICU
51	66	6-Jan-05	CPAP	56	81	COPD	CPAP	B,I	44	99	COPD	ACS ?	ETI	B,I,F,S	ICU 8, Hosp 13	d/c alive
52	56	9-Jan-05	UC	40	83	COPD, CHF	BMV	N,B	28	96	CHF	Pneumonia	ETI	N,F,M,B,I,A	ICU 9, Hosp 9	died
53	84	17-Jan-05	UC	44	80	Asthma, CHF	BMV	N	*	84	CHF	none	ETI	N,F	ICU 4, Hosp 9	d/c alive
54	75	22-Dec-04	CPAP	36	*	SOB NYD	CPAP	NONE	16	99	COPD	none	CPAP	B,I,S,A	ICU 2, Hosp 7	d/c alive
55	78	27-Feb-05	CPAP	40	82	CHF	CPAP	N	28	95	CHF	none	CPAP	N,F	ICU 2, Hosp 4	d/c alive
56	81	27-Mar-05	UC	40	69	SOB NYD	BMV	NONE	*	*	COPD	Pneumonia	ETI	B,A,D	Died in ED	died
57	68	11-Apr-05	CPAP	42	68	CHF	CPAP	M,F	32	96	CHF	none	CPAP	N,F,A,B,I	ICU 0, Hosp 5	d/c alive
58	67	20-Apr-05	CPAP	40	67	CHF	CPAP	N,M	23	99	CHF	none	CPAP	N,F	ICU 7, Hosp 7	d/c alive
59	70	6-Jun-05	UC	44	82	Pneumonia	o2 by mask	B,I	28	86	Pneumonia	COPD	O2 by mask	A	ICU 0, Hosp 18	died
60	64	2-Aug-05	UC	40	72	CHF	o2 by mask	N,F	40	91	CHF	none	CPAP	N,F	ICU 0,5	d/c alive
61	45	7-Sep-05	UC	30	95	Asthma	o2 by mask	B,I	24	100	Asthma	none	O2 by mask	B,I,S	ICU 0, Hosp 2	d/c alive
62	71	7-Sep-05	UC	36	78	COPD, Pneumonia	o2 by mask	B,I	38	70	COPD	CHF, Pneumonia	O2 by mask	B,I,F,N	ICU 0, Hosp 8	d/c alive
63	63	3-Mar-06	CPAP	36	50	CHF	CPAP	N	36	97	CHF	COPD, Pneumonia	CPAP	N,F	ICU 3, Hosp 12	d/c alive
64	54	5-Mar-06	UC	24	50	Asthma	ETI	B,I	tubed	99	Asthma	none	Ventilator	B,I,S,N	ICU 36, Hosp 47	d/c alive
65	72	7-Feb-04	UC	36	88	CHF	o2 by mask	N,F	36	*	COPD	CHF, Pneumonia	CPAP	B,F,A	Died in ED	died
66	65	22-Sep-05	UC	32	83	COPD	o2 by mask	B,I	30	97	COPD	none	O2 by mask	B,I,S	Overnight in ED	d/c alive
67	78	19-Dec-05	UC	28	72	CHF	o2 by mask	N,F,M,B	26	*	CHF	none	O2 by mask	N,F	ICU 0, Hosp 5	d/c alive
68	44	24-Oct-05	UC	40	*	Asthma	BMV	B,I	25	100	Asthma	none	ETI	B,I,S	ICU 15, Hosp 15	d/c alive
69	49	18-Jul-04	UC	38	64	COPD	ETI	B,I	tubed	100	COPD	none	Ventilator	B,I,S,D	Died in ED	died
70	58	31-Jul-04	UC	44	75	CHF	o2 by mask	N,B	39	99	CHF	Pneumonia	O2 by mask	N,F	ICU 3, Hosp 12	d/c alive
71	43	16-Jan-04	CPAP	28	99	Asthma	CPAP	B,I	48	*	Asthma	none	CPAP	B,I,S	ICU 0, Hosp 3	d/c alive

*=missing data
4=Refused Long Consent
24=Refused Long Consent

N=Nitro
F=Fluroside
M=Morphine
B=Beta Agonists
I=Ipratropium Bromide
A=Antibiotics
S=Steroids
D=Dopamine or Dobabutime

Figure E1. Location/time of tracheal intubation or death.